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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/064,000	ELIA, JAMES P.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *403-405 and 407-412* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *403-405 and 407-412* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Brief filed on 08/20/2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

2. Claims 403-405 and 407-412 are under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Rejection Claims 403-405 and 407-412 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. Applicant's arguments filed 08/20/2009 have been fully considered but they are not persuasive. The rejection of record finds that the recitation in claim 403, step (b) "forming a bud" creates a lack of clarity as to whether the recited step requires action on the part of the practitioner of the method to form a bud. The most straightforward interpretation of step (b) "forming a bud", is that the practitioner is being instructed to do something. Likewise, the claim recites "(c) growing said desired artery from said bud", which also indicates that the practitioner is instructed to do something. The rejection of record finds that these instructions are unclear because the specification does not provide any teaching specifically directed to forming a bud.

5. Applicant cites the specification at page 31, lines 18-26, and page 39, Example 3, as providing teaching directed to forming a bud. The cited sections of the specification are reproduced here:

Page 31, lines 18-26:

> In another embodiment of the invention, instead of transplanting a bud 122 into the jaw of a patient, a quantity of genetically produced living material which causes bud 122 to form in the alveolar bone can be placed at a desired position in the alveolar bone such that bud 122 is morphogenetically created in vivo and grows into a full sized tooth. Instead of forming an opening 123, a needle or other means can be used to simply inject the genetically produced living material into a selected location in the alveolar bone. As would be appreciated by those skilled in the art, genetically produced materials can be inserted in the body to cause the body to grow, reproduce, and replace leg bone, facial bone, and any other desired soft and hard tissue in the body.

Page 39, Example 3:

> Example 1 is repeated, except that the germinal cells are obtained from soft periodontal ligament tissue immediately adjacent the apex of the immature forming root of a patient's tooth. These cells are selected because they are actively transcribing root structure and contain active growth and transcription factors which facilitate the formation of the tooth germ.

6. These sections do indeed mention a "bud". The context is directed to a tooth bud. Page 31 includes a general assertion that "genetically produced materials" can be applied in similar methods to cause the body to grow any other desired soft and hard tissue. Applicant summarizes this as teaching "that once the composition required for forming the desired tissue is implanted in the patient at a desired location *a bud is formed* which grows via morphogenesis into the desired tissue" (emphasis added here). Applicant does not seem to be arguing that any special act required by the practitioner of the method to form a bud, as indicated by the passive voice, "*a bud is formed.*" Applicant relies on this teaching to argue that, "A skilled person having experience in the medical arts reading the instant specification would understand that the formation of a bud/primordium is the foundation for human organogenesis." All of this is a continuation of Applicants previous argument that "it is clear from the specification that the only step required by the practitioner is that of injecting stem cells into a selected site in a patient's body." Thus, Applicant acknowledges that although step (b) (and, by implication, step (c)) has the form of a method step, the actual intent is to recite an intended outcome. The specification does not teach that there is any special act required by the practitioner of the method to form a bud, or to grow an artery from said bud. The specification teaches that "germinal cells are obtained from soft periodontal ligament tissue" may "facilitate the formation of the tooth germ", which, at most, generically corresponds to step (a). (The clarity and specificity with which this suggests implanting *stem cells to grow an artery* is a separate issue.) In the exemplified growth

of a new tooth, formation of a bud is not something over which the practitioner has any control. The specification is silent as to the formation of an *artery bud*. It is not clear, therefore, what is meant when claim 403 recites a method step (b) instructing the practitioner to form a bud followed by a step (c) which instructs the practitioner to grow an artery from said bud.

7. The lack of clarity is underscored in the prosecution history of the instant case. In response to a provisional nonstatutory double patenting rejection of the instant claims over the claims of copending application Serial No. 10/179,589, Applicant has argued, "It is pointed out that the claims in the instant application require the preliminary step of forming a bud in the body of the patient which then grows into an artery, while the claims co-pending application Serial No. 10/179,589 have no such requirement. Hence the claims presented in the respective applications are not drawn to identical subject matter" (Brief filed on 11/24/2008, p.37b). Applicant now argues, (Brief, p. 51) that "The PTO's statement at page 36, ¶41 of the Rejection that, "Therefore, Applicant indicates that step (b) inherently occurs every time step (a) is performed" is not correct. Such statement is only correct when a bud is formed." These arguments suggest that (1) Applicant intends that claims that recite a step of forming a bud (*i.e.* the instant claims) are substantially different from claims that recite the same step (a) without a step of forming a bud (*i.e.* the claims application 10/179,589) and (2) when step (a) is performed, there are instances where a bud is formed and instances where a bud is not formed. Applicant's argument regarding double patenting and argument against the rejection under 35 U.S.C. 112, second paragraph are mutually exclusive, they cannot both be persuasive. If step (b) of instant claim 403 merely recites an inherent outcome of step (a), then step (b) cannot distinguish this claim from copending claim 161, which recites an identical step (a). If step (b) of instant claim

403 is intended as a separate step in which the outcome of the step may vary depending on action taken by the practitioner of the method, then the claim is unclear because the specification does not teach this separate step.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Rejection of Claim 404 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. Applicant's arguments filed 08/20/2009 have been fully considered but they are not persuasive. The rejection of record finds that claim 404, which first appeared in the record in the amendment of 11/03/2006, introduces new matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection finds no support for the combination of limitations that includes growing an artery by administration of stem cells to a damaged site in a leg of a patient in the specification as originally filed.

10. It is not the general concept of 'injecting stem cells' that is being rejected as lacking written description. Likewise, it is agreed that the specification provides support for the concept of growing an artery. The rejection of record finds that, while support for selecting these two concepts into a single method, i.e. 'injecting stem cells to grow an artery' is tenuous; the concept

of first combining these limitations and then further adding the limitation of placing the cell at a damaged site in a leg of a patient is non-existent.

11. Applicant argues (p.10). "It is clear that all the claimed limitations appear as words in the specification." This has been addressed in the record. It has been established that pages 10, 18, 20, 21, 31, 32, 37, 40, 41, and 52 generically teach organs or tissues, but not the recited artery. Examples 15 and 16 (pages 41-42) suggest that stem cells from bone marrow or blood may be genetically engineered to grow kidneys, not the claimed species of organ. Example 17 has a section directed to formation of an eye, but also includes a teaching (p.45) directed to artery formation which suggests "injecting a gene or other genetic material" (lines 2-3), "VEGF genes" (lines 10-11) or "VEGF proteins "(lines 13-15); no cells are mentioned. Pages 47-48 mention stem cells, among other cell types, and an artery, among other organs, but does not recite a damaged site in a leg. Example 18 (p.53) mentions legs, but teaches the use of recombinant DNA and does not reasonably suggest the use of any kind of cell to grow an artery. Examples 19 (p.55-56) and 36 (page 62) mention coronary arteries, not an artery in a damaged site in a leg, and like Example 18, Examples 19 and 36 teach the use of recombinant DNA and do not reasonably suggest the use of any kind of cell to grow an artery. Applicant's specification did not disclose with specificity which cells would or would not work for growing an artery. Cells are put forth for a variety of purposes. In some places it could be any cell. In others it is a skin cell that has undergone a mysterious process of dedifferentiation and redifferentiation, a "germinal cell", "or in some cases stem cells" (pages 47-48). The cells are described as being "multifactorial and nonspecific", which does not provide any meaningful limitation as to the cells to use (see paragraphs 6-25 of the office action mailed 07/24/2007).

12. Applicant has argued that one of skill in the art would infer "stem cells" from sections of the specification that do not even mention any kind of cell. Applicant's basis for this assertion relies on the notion that the broad definition of "growth factors" found in the specification at pages 20-21 conveys the concept of "cells" or specifically "stem cells" as species with the genus of growth factors. It is noted that Applicant's first reply in the prosecution of this case, filed 12/16/1999, dealt extensively with the scope of materials, including "growth factors", that can be used to grow soft tissue, but never once mentioned any kind of stem cell as having this capability. Claims reciting placing a "growth factor" into a body of a human patient were introduced into this application on 02/15/2001, which prompted a requirement for species election. Twenty-four patentably distinct species (a-x) of "growth factor" were found in the instant disclosure, from which Applicant was required to elect a single product or structure (requirement for restriction/election mailed on 02/24/2004). The list of species did not include "cells" or "stem cells". Thus, to clarify the record, Applicants' current allegation that that "the PTO, in making restriction requirements prior to and subsequent to the date of the instant Rejection, has consistently identified genes and cells as species of the genus "growth factor"" (Brief, page12) is incorrect. Furthermore, the fact that an examiner presented with claims in a continuing application that recite "cells" as a species of "growth factor" might take that recitation at face value and restrict accordingly, prior to thorough examination of the specification, is immaterial to the present case. The requirement for restriction/election mailed on 02/24/2004 did not include a species of "cells" or "stem cells" because "cells" or "stem cells" are never clearly set forth as species of growth factor anywhere in the instant specification. Cells (and certainly not stem cells) are not included in the definition of growth factor (specification pages

20-21). The expression "growth factors, such as stem cells" does not appear anywhere in the specification, it is never found in peer-reviewed non-patent literature, or in any patent literature, it only appears in arguments of counsel in this case and others with the same applicant. Use of the term "growth factor" to mean "cell" (or "cell" to mean "growth factor") is outside of the normal meanings of these terms. In this regard, Applicant (Brief, bridging pages 11-12) argues:

> "the definition found in the Alberts et al. publication definition of "growth factor" cited and made of record by the present PTO Examiner in co-pending Application Serial No. 09/836,750 and entitled, Molecular Biology of the Cell, 4th Ed., Chapter 17 (attached hereto as Exhibit A and hereinafter "Alberts"). Alberts' definition of a growth factor is consistent with Appellant's definition found on page 43, lines 18 and 19 of the specification, "Growth factors control cell growth, division, differentiation, migration, structure, function, and self-assembly."

It is clear however, that both the Alberts definition and the quote from the instant specification teach that a growth factors *act upon cells*, not that growth factors *are* cells.

13. The point here is not that it is abhorrent or technically incorrect for the Applicant to attempt to define a class of growth factors that includes genes and bone marrow stem cells. The point is that any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). Applicant asserts (Brief, bridging pages 11-12) that ¶¶5-7 of the Declarations of Drs. Wheeler, Finley, and Lorincz, ¶6 of the Declaration of Dr. Heuser, the Supplemental Declaration of Dr. Lorincz provide definitive answers to whether one experienced in the medical arts reading the specification would understand that Applicant's usage of the term growth factor was intended to include compositions comprising genes and bone marrow stem cells. This is not persuasive because the Declarations of Drs.

Wheeler, Finley and Lorincz, filed on 02/15/2001 do not mention administration of any kind of cell for any purpose. These Declarations were directed mainly to the concept of a bud, and the Declarants referenced only the administration of protein growth factors or expression plasmids that encode protein factors. The concept that the genus of growth factors could include cells first appeared in the Declaration of Dr. Heuser, the Supplemental Declaration of Dr. Lorincz, filed 06/26/2006, wherein the Declarants considered newly entered claims reciting cells. There is no evidence in the record that any Declarant recognized a concept that cells are a species of growth factor in the specification as filed.

14. In response to the requirement for election of species, Applicant elected, without traverse, (03/03/2004) species a) "living organism", which was subsequently determined to include "cells". The notion that the specification aims to include "cells" within the genus of growth factors relies only on the fact that cells are, reasonably, "living organisms", which are listed as potential growth factors (specification page 20). This line of reasoning has been deemed sufficient to permit examination of claims that recite "cells" when the species "living organism" had been elected. Applicant's suggestion that the present PTO Examiner has decided to not accord full faith and credit to prior PTO determinations (Brief, p.12) is belied by the fact that the Examiner has continued to work with the prior decision to permit Applicant to shift inventions to a species that was not previously presented, after an election had been made. No prior determination indicates that the PTO has held that a method of using *stem cells* for the particular purpose of growing an artery in a leg has been described.

15. The record is clear that the choice of "stem cell" as a species of growth factor was not an easy one to make; it involves first selecting "cells" from within an enormous genus of asserted

growth factors, and then selecting "stem cells" from within the genus of cells. This is only one of the selections that must be made to arrive at claim 404. The combination recited in claim 404 additionally requires the selection of "artery" from the genus of organs and soft tissues and selection of "a damaged site in a leg" from the genus of "the body" as the site where the artery is to be grown. The specification does not suggest, contemplate, or *reasonably* lead to the specific use of stem cells together with the specific location in the leg, as required by claim 404. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species). In *Purdue Pharma L.P. v. Faulding Inc.*, 230 F. 3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000), the court noted that with respect to *In re Ruschig* 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure."

16. Applicant has correctly pointed out that to comply with the written description requirement of 35 U.S.C. 112, first paragraph, 'the applicant must.., convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.' Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. One cannot ignore *reasonable clarity*. The mere presence of all of the limitations at various locations in the specification does not constitute adequate written description. The specification as filed does not contemplate the claimed combination of limitations. Taken as a whole and in view of

Applicant's cited pages therein, the specification does not reasonably lead the skilled artisan to the recited combination of the agent to be administered, the desired result, and the site of administration. Even if one of skill in the art could infer the claimed method by combining the disconnected teachings of the specification, at best this would only render claim 404 obvious in view of the specification. Disclosure which merely renders the later claimed invention obvious is not sufficient to satisfy the written description requirement of 35 U.S.C. 112, first paragraph. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1505, 41 USPQ2d 1961 at 1966. The introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 involves narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure, which is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. Therefore the introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 constitutes new matter.

17. Rejection of Claims 403-405 and 407-412 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. Applicant's arguments filed 08/20/2009 have been fully considered but they are not persuasive.

18. It is first noted that Applicant has separately argued claims 403, 411, and 412, claims 404 and 405, and claims 407-410. The rejection of record finds that elements that are essential and common to all of the claims are not enabled by the disclosure. No recited limitation rescues any claim from lack of enablement. Therefore, this office action will provide a single rejection and response to arguments for all of claims 403-405 and 407-412.

19. Applicant (Brief, p. 13) submits that there are three major points to consider when determining whether the instant specification contains a disclosure that would have enabled a skilled person in the medical art to make and use the claimed invention within the purview of the statute. The points are: 1) the content and guidance provided in the specification disclosure; 2) the knowledge in the art at the time the application was filed; and 3) the skill level in the art. The rejection of record has consistently acknowledged that the level of skill in the art is high.

20. With regard to points 1) and 2), Applicant identifies U.S. Patent No. 5,980,887 to Isner et al. (hereinafter "Isner '887"; of record) and the Asahara et al. February 14, 1997 publication in Science entitled, "Isolation of Putative Progenitor Endothelial Cells for Angiogenesis," (hereinafter "Asahara"; of record), and U.S. Patent No. 5,328,470 to Nabel et al. (hereinafter "Nabel" and of record) as examples of the state of the prior art at the time of Applicant's invention (Brief, p. 15). Applicant argues that the instant disclosure distinguishes over prior or contemporary art by employing different cells to achieve different results (Brief, p. 15). Thus, Applicant agrees that the state of the art at the time the instant application was filed did not include any support or disclosure of the growth of new arteries by administering stem cells. Applicant asserts (p.14) that the instant specification describes “a class of claimed and unclaimed growth factors that broadly and specifically include genes, nucleic acids, a patient's own cells (autologous cells), or universal cells, e.g., stem cells (global mononuclear bone marrow cells), etc., all of which are described to promote tissue growth through differentiation and morphogenesis." This disclosure is said to provide “a scope of enablement which includes stem cells broadly ([specification] pages 37, 48, 50, and 51) and bone marrow mononuclear stem cells specifically ([specification] pages 40-42). Such disclosure is commensurate in scope with the

subject matter of the claims at issue." Similarly, Applicant argues (p. 15) "One skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that the claimed invention distinguishes from Isner '887 by describing using unfractionated (global) bone marrow mononuclear cells and in achieving a different functional outcome." Applicant further argues that post-filing publications of record, including Strauer et al. Circulation 106:1913-1918, 2002 (hereinafter "Strauer") and U.S. Patent No. 7,097,832 to Kornowksi et al. (hereinafter "Kornowski") disclose the same results using the same cells, thus confirming Applicant's disclosed and claimed results (Brief, p. 23-25, p. 40).

21. This rejection finds that the present application does not provide an enabling disclosure or an accurate prediction of the methods and results that were later achieved by others. Therefore, the post-filing references do not confirm Applicant's disclosed and claimed results but instead, the post-filing references constitute evidence of the further act of invention that was required before achieving any growth of an artery by administering cells. This office action will address Applicant's points 1) and 2) along with the predictability or lack thereof in the art, the breadth of the claims, and the quantity of experimentation needed.

22. The rejection of record has found that *the breadth of the claims* and the *amount of direction or guidance present and the presence or absence of working examples* are the principal factors that speak against the enablement for the claims under consideration. The claims are broad as they recite the administration of "stem cells", which includes embryonic stem cells, neural stem cells, amniotic epithelial cells, hematopoietic stem cells, and mesenchymal stem cells, to mention those cited in references of record. Therefore, the question of which cells would or would not work for growing an artery is critical to breadth of the claims and to enablement of the

general methods. As noted previously, even if interpreted in Applicant's most favored light, the most precise description of the cells to be administered in the instantly claimed methods is "bone marrow stem cells". Thus, the breadth of the term "stem cell" cannot not be supported by an enabling disclosure.

23. The rejection of record finds that the instant specification did not disclose with specificity which cells would or would not work for growing an artery. In the Brief, bridging pages 20-21, Applicant focuses on the words "or would not work". Applicant characterizes this as an "assertion that an applicant must disclose with specificity which cells *would not form an artery* is and asserts that an applicant is not required to provide information that would *not* enable one skilled in the art to make and use such invention; i.e., to form an artery" (Brief, bridging pages 20-21, emphasis added). It has been noted, however, that the specification mentions cells in many contexts and cells are put forth for a variety of purposes. In some places it could be any cell. In others it is a skin cell that has undergone a mysterious process of dedifferentiation and redifferentiation. It might be a "germinal cell" "or in some cases stem cells". The cells are described as being "multifactorial and nonspecific", which does not provide any meaningful limitation as to the cells to use (see paragraphs 6-25 of the office action mailed 07/24/2007). The instant claims recite administration of "stem cell" (all claims), "stem cell harvested from bone marrow" (claim 407 and dependents) or "stem cells harvested from blood" (claim 409 and dependents). For enablement, the specification must direct the skilled artisan to select these recited cells and teach the skilled artisan how to use them to grow an artery. Thus, the finding that "the instant specification did not disclose with specificity which cells would or would not work for growing an artery" has exactly the same meaning and import if "or would not" is

deleted: the instant specification did not disclose with specificity which cells would work for growing an artery.

24. Applicant generally argues that the instant specification teaches administration of unfiltered (global) bone marrow mononuclear cells. This teaching is asserted to distinguish the instant specification from contemporary art and to be consistent with, and confirmed by, post-filing disclosures. Examples include (emphasis added):

Brief, page 15-16:

> One skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that **the claimed invention distinguishes from Isner by describing using unfractionated (global) bone marrow mononuclear cells and in achieving a different functional outcome.** There is no basis in fact for determining that a fractionated population, such as EC progenitor cells, is disclosed by Appellant….The collection, handling, and reimplantation of HSCs are so well known and notorious in the medical arts that the Board should take Official Notice of same.

Brief, page 23-24:

> The PTO also alleged that the expressions "stem cells harvested from bone marrow" and "stem cells harvested from blood" were typically understood to refer to the CD34+ fraction. One only has to note that the post-filing date Strauer et al. publication in Circulation entitled, "Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans" and (hereinafter "Strauer" and of record [Strauer 2002]) and U.S. Patent No. 7,097,832 to Kornowksi et al. (hereinafter "Kornowski" and of record) had no such misunderstanding of the term "stem cell."… In the previously mentioned complete internet article entitled, "Progenitor Cell Transplantation and Function following Myocardial Infarction," Dr. O'Neil acknowledges that **there are two schools of thought as to which cells to use-unfiltered bone marrow (Appellant, Strauer, and Komowski) or CD34 positive cells (Isner).** In any event, one skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that the claimed invention distinguishes from the CD34+ fraction of Isner by describing using unfiltered (global) bone marrow mononuclear cells. As pointed out earlier, there is no basis in fact for the PTO to determine that the instant specification provides guidance to one skilled in the art for implanting anything other than the entire array of bone marrow derived cells harvested from the patient's bone marrow or blood.

25. The instant specification refers to bone marrow only in the sentence, "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques", which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10). It has been pointed out that the expression "Stem cells harvested from the bone marrow, the blood of the patient, or from cell culture techniques" is not equivalent to "unfractionated (global) bone marrow mononuclear cells" in its ordinary meaning in the art. (Office action 02/26/2009, paragraphs 15-16). The Rowley *et al*. reference (of record) was cited as evidence that the expressions "stem cells harvested from the bone marrow" and "stem cells harvested from the blood" were typically understood to refer to the CD34+ fraction. It is further noted herein that when Janssen *et al*., (Journal of Hematotherapy, 1:349-359 (1992)) described use of an apparatus for processing of bone marrow stem cells, the definitive demonstration that "stem cells" were obtained was by identification of CD34+ cells or by colony forming assays; prior to that the cells were simply referred to as fractions obtained in a step of isolation (mononuclear, Ficoll gradient, buffy coat, etc., see Figures 10 and 11 and Table 1). Thus, "*stem cells* harvested from the bone marrow" would be understood to connote a sub-population of bone marrow cells, not "unfractionated (global) bone marrow mononuclear cells".

26. Applicant attempts to counter this evidence by asserting that Strauer (2002, of record) and Kornowski (U.S. Patent No. 7,097,832; of record) "had no such misunderstanding of the term "stem cell"" (Brief, page 23). The Examiner agrees with Applicant's assertion that Strauer and Kornowski had no misunderstanding of the term "stem cell." Strauer and Kornowski had no misunderstanding of the term "stem cell." The Kornowski '832 patent teaches that "autologous bone marrow acts as a "natural source of mixed angiogenic cytokines" which "provide a mixture

of potent interactive growth factors" (column 4, lines 45-49). Note that Kornowski refers to "bone marrow" and to "the cells" in bone marrow, but not specifically to the *stem cell* population from bone marrow. Kornowski never, even once, refers to the preparation to be administered to promote arteriogenesis as "stem cells". Similarly, Strauer et al. acknowledge that bone marrow *contains* multipotent stem cells (p. 1913, paragraph bridging columns) but they also cite evidence showing that "environmentally dictated changes of fate (transdetermination) are not restricted to stem cells" (p. 1916, right column). Strauer et al. carefully referred to the preparations that were administered as "mononuclear bone marrow cells" or simply "bone marrow cells (BMC)". See for example, the first sentence of the discussion (p. 1915, emphasis added):

> "The present report describes the first clinical trial of intracoronary, autologous, **mononuclear BMC** transplantation for improving heart function and myocardial perfusion in patients after acute MI."

The population of bone marrow mononuclear cells used by Strauer (2002, of record) comprised only 2.1% CD34-positive cells (Strauer, p. 1914, paragraph bridging the columns). Thus, Strauer and Kornowski had no misunderstanding of the term "stem cell." It is evident from Strauer and Kornowski that the critical cell in the preparations they administered may not be any previously characterized stem cell; it may not even be a *stem cell* at all but rather some other previously uncharacterized growth factor secreting cell. Strauer and Kornowski acknowledged this by **careful use of terminology coupled with actual demonstrations of how the cells were prepared and the outcomes that were achieved**.

27. In contrast, the teaching of the instant specification does not give the skilled artisan clear instructions for what to do. Applicant argues that "The failure of the specification to teach separating and excluding any given fraction of mononuclear bone marrow stem cells is consistent with the requirement for using an unfractionated bone marrow composition and constitutes a reasonable reading of the specification" (Brief, p. 24). In view of the terminology of the art, however, the recitation of "stem cells harvested from bone marrow, the blood of the patient, or from cell culture techniques", together with failure to mention any preparation details is consistent with a teaching of a requirement for CD34+ stem cells. In view of the vague teaching of the specification, Applicant could devise an argument to fit any subsequent disclosure. That is, if it had turned out that the CD34+ population of stem cells was sufficient to promote artery growth, Applicant could claim to have predicted that outcome by arguing that, of course, use of the CD34+ population is implicit in "stem cells harvested from bone marrow, the blood of the patient, or from cell culture techniques". Such argument would have equal validity (or lack thereof) to the argument Applicant is presently making.

28. Similarly, the vague teaching of the specification is being used by Applicant to make contradictory assertions about the prior art and the need for the instant application to provide guidance for the claimed methods. As noted, Applicant has argued that the cells disclosed in Isner '887 or the Asahara are distinct from the stem cells recited for use in the instant claims. Yet Applicant also asserts that one of skill in the art would rely on these references to teach that fact that stem cells home to loci of ischemic tissue and, therefore, the specification need not teach anything more about how to grow an artery other than to direct the artisan to use stem cells (Brief, p. 26). Thus, Applicant's argument requires that the skilled artisan should expect that by

"stem cell" Applicant means something similar to the endothelial progenitor cells in Isner '887 or Asahara but yet different in being able to form complete arteries. The specification does not provide the teaching to support this argument. If the stem cells of the instant specification and claims are different from those of Isner '887 or Asahara, how would the skilled artisan know that they share the property of homing to loci of ischemic tissue in the absence of an actual demonstration of that capability?

29. Applicant argues (Brief, p. 21):

> The specification teaches on pages 40-42, 47, and 48 utilizing autologous stem cells harvested from bone marrow and blood of the patient (self-cell therapy) or from cell cultures (allogenic) to grow organs, i.e., arteries, by differentiation and morphogenesis (page 48). There can be no doubt that the specification teaches that bone marrow cells promote the growth of organs. Further, the specification on page 50 specifically discloses that implanted pluripotent growth factors direct adjacent cells to reconstruct body parts along genetically predetermined pathways.

30. Applicant similarly argues (Brief, p. 22):

> Turning more specifically to the PTO's allegation that the subgenus "stem cells" is large and thus does not advise the skilled person which stem cells to use or not use, Appellant points out that the specification describes the subject matter of claims 407- 410, stem cells harvested from bone marrow and stem cells harvested from blood, at pages 40-42, and pages 47-52 wherein the specification discloses using a patient's own stem cells for growing multiple described organ species through differentiation and morphogenesis. Furthermore, the organ species artery is specifically disclosed as a desired target organ on page 52 and, as stated previously, pluripotent stem cells are described at page 50.

31. The cited sections of the specification are reproduced here. Each section will be followed by an examination of the respective teachings which are asserted to provide guidance for the claims under consideration:

> Page 40, line 20 to Page 42, line 27
>
> EXAMPLE 11

MSX-1 and MSX-2 are the homeobox genes that control the generation and growth of a tooth. A sample of skin tissue is removed from the patient and the MSX-1 and MXS-2 homeobox gene(s) are removed from skin tissue cells. The genes are stored in an appropriate nutrient culture medium.

BMP-2 and BMP-4 growth factors are obtained by recombinant or natural extraction from bone.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

MXS-1 and MXS-2 transcription factors are obtained which will initiate the expression of the MXS-1 and MXS-2 homeobox genes.

The MXS-1 and MXS-2 transcription factors, BMP-2 and BMP-4 bone morphogenic proteins, and MXS-1 and MXS-2 genes are added to the nutrient culture medium along with the living stem cells.

EXAMPLE 12

Example 11 is repeated except that the transcription factors bind to a receptor complex in the stem cell nucleus.

EXAMPLE 13

Example 11 is repeated except that the MXS-1 and MXS-2 transcription factors are not utilized. The transcription of the MXS-1 and MXS-2 homeobox genes is activated by applying an electric spark to the nutrient culture medium.

EXAMPLE 14

[0153] Example 13 is repeated except that the stem cells are starved and the transcription of the MXS-1 and MXS-2 homeobox genes is activated by applying an electric spark to the nutrient culture medium.

EXAMPLE 15

WT-1 and PAX genes are obtained from a sample of skin tissue is removed from the patient. The genes are stored in an appropriate nutrient culture medium. PAX genes produce PAX-2 and other transcription factors.

BMP-7 and other kidney related BMP growth factors are obtained by recombinant

or natural extraction from bone.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

[The WT-1 and PAX genes, and BMP-7 and other kidney BMPS are added to the nutrient culture medium along with the living stem cells.

A primitive kidney germ is produced. The kidney germ is transplanted in the patient's body near a large artery. As the kidney grows, its blood supply will be derived from the artery.

EXAMPLE 16

The Aniridia gene is obtained from a sample of skin tissue is removed from the patient. The gene(s) is stored in an appropriate nutrient culture medium.

Aniridia transcription factor (activates expression of the Aniridia gene) and growth factors (function to help stem cells differentiate during morphogenesis to form an eye) are obtained.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

The Aniridia transcription factor and growth factors and the Aniridia gene are added to the nutrient culture medium along with the living stem cells.

A primitive eye germ is produced. The kidney germ is transplanted in the patient's body near the optic nerve. As the kidney grows, its blood supply will be derived from nearby arteries.

EXAMPLE 17

The Aniridia gene is obtained from a sample of skin tissue is removed from the patient. The gene(s) is stored in an appropriate nutrient culture medium.

Aniridia transcription factor (activates expression of the Aniridia gene) and growth factors (function to help stem cells differentiate during morphogenesis to form an eye) are obtained and added to the nutrient culture medium.

> An eye germ develops. A branch of the nearby maxillary artery is translocated to a position adjacent the eye germ to promote the development of the eye germ. The eye germ matures into an eye which receives its blood supply from the maxillary artery.

32. These reproduced sections of pages 40-42 comprise the only references to bone marrow in the entire specification. The specification refers to bone marrow only in the sentence, "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques", which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10; Examples 11, 15, and 17). These Examples assert that whole organs can be grown from bone marrow stem cells. Applicant apparently believes that the skilled artisan should take from these pages only the fact that they mention "cells" and "organs" but then ignore what they actually say about which cells to use, which organs to grow, or how to perform methods of using the cells. In Examples 11-17 the artisan is instructed to remove genes from skin tissue of a patient and then the artisan is given the nonsensical instruction to store the genes in nutrient culture medium. (Actually, this instruction might make sense if one believes that nucleic acids and cells are not different from one another, as Applicant has repeatedly argued, e.g. Brief p. 32, "incorrect conclusion that gene therapy and cell therapy have different status in the art".) The genes are then to be added to culture medium along with stem cells; this apparently is meant to suggest a transfection procedure to genetically engineer the cells. This is taught to result in growth of a tooth, kidney, or eye, depending on the genes used. These examples do not set forth credible procedures to produce the results asserted within the examples. A cell that is capable of differentiation and morphogenesis to form an entire organ, such as an eye, would indeed be pluripotent, but bone marrow stem cells are not known to have this capability, even under the influence of an expressed Aniridia gene. Thus, Applicant's argument that "There can be no doubt

that the specification teaches that bone marrow cells promote the growth of organs" (Brief, p. 21) is not persuasive because bone marrow cells simply do not do the things the specification teaches that they can do. As noted in the first office action on the merits in this case, mailed 05/27/1999, at paragraph 5:

> The method of forming an organ in the body, as well as the composition for producing an organ for implanting in the body would not be accepted as obviously valid by one of ordinary skill in the art. The allegation that organs can be created and grown either in vivo or in vitro borders on the incredible to one of ordinary skill in the art.

Furthermore, these examples do not even mention growth of an artery as recited in the instant claims. Nevertheless, Applicant expects the skilled artisan to take the mention of bone marrow in the context of Examples 11-17 and combine it with the mention of "growth of an artery" (among other possible outcomes) on page 48 to arrive at enabling support for the instant claims.

33. Specification Page 47, line 22 to Page 48, line 15:

> Organs and/or tissues can be formed utilizing the patient's own cells. For example, a skin cell(s) is removed from the intraoral lining of a cheek. The cell is genetically screened to identify DNA damage or other structural and/or functional problems. Any existing prior art genetic screening technique can be utilized. Such methods can utilize lasers, DNA probes, PCR, or any other suitable device. If the cell is damaged, a healthy undamaged cell is, if possible, identified and selected. If a healthy cell can not be obtained, the damaged cell can be repaired by excision, alkylation, transition or any other desired method. A growth factor(s) is added to the cell to facilitate dedifferentiation and then redifferentiation and morphogenesis into an organ or function specific tissue. Any machine known in the art can be used to check the genetic fitness of the organ and its stage of morphogenesis. A cell nutrient culture may or may not be utilized depending on the desired functional outcome (i.e., growth of an artery, of pancreatic Islet cells, of a heart, etc.) or other circumstances. Replantation can occur at any appropriate stage of morphogenesis. The foregoing can be repeated without the patient's own cells if universal donor cells such a germinal cells are utilized. Germinal cells do not require a dedifferentiation. They simply differentiate into desired tissues or

> organs when properly stimulated. Similarly, the DNA utilized in the foregoing procedure can come from the patient or from any desired source.
>
> During reimplantation one of the patient's own cells is returned to the patient. During implantation, a cell not originally obtained from the patient is inserted on or in the patient.
>
> In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.

34. Applicant's chosen section of pages 47-48 begins with a general statement that organs and/or tissues can be formed utilizing the patient's own cells. While one of skill in the art might expect that "patient's own cells" *could* refer to "stem cells harvested from bone marrow", among other possibilities, the next sentence steers the artisan away from that embodiment: "For example, a skin cell(s) is removed from the intraoral lining of a cheek." It is this skin cell that is the subject through all the description leading up to the mention of artery formation. The artisan is instructed to screen the skin cells for DNA damage, to check genetic fitness, and repair damaged cells. No information is given as to what constitutes "genetic fitness", what genes are involved, or how cells are to be induced to affect the desired repair. The method then suggests the addition of some unknown and undefined growth factors after which the cells can undergo processes of dedifferentiation and redifferentiation followed by morphogenesis into any desired organ or tissue. No such growth factor regimen is known in the art, and the specification does not teach one. In view of the definition of "cell nutrient culture" (specification p.41), the instruction that, "A cell nutrient culture may or may not be utilized" refers to the potential use of novel combinations of growth factors, ECM, nutrients, and vitamins that are suggested to be able to cause cells to dedifferentiate, redifferentiate and form any organ or tissue. The specification,

however, does not teach any specific factors or combination of factors that cause any cell to form an artery.

35. On page 48, "Germinal cells" are suggested as an alternative to the dedifferentiated skin cells. The vagueness of the term "germinal cells" has been addressed in the record. The term "germinal cells" does not refer to a specific kind of cell, but it is understood to be a generic term for a cell from which other cells proliferate. This functional definition does not guide the artisan as to where or how to obtain the cells that can be used to grow an artery. Thus, by suggesting the use of "germinal cells", the specification essentially gives the skilled artisan the tautological instruction to grow an organ by using a cell capable of growing an organ. The context on page 48 indicates that "germinal cell" is meant to connote something distinct from a stem cell—"germinal cells" and "stem cells" are presented as alternatives connected by "or", not as synonyms or related as genus and species. "Germinal cells" are suggested to differentiate into desired tissues if properly stimulated. How to properly stimulate them to form an artery or any other organ is not disclosed.

36. In summary, pages 47-48 of the specification suggest the examination of fitness of unknown genes by unidentified criteria, the use of unidentified machines, unknown methods of effecting DNA repair, the addition of unknown and undefined growth factors, ECM components, nutrients, and/or vitamins to cause cells to undergo dedifferentiation, redifferentiation, and morphogenesis into *any desired organ or tissue*, and unidentified "germinal cells". These teachings are found to be inadequate for teaching the skilled artisan to *how to* grow an artery. Furthermore, the skilled artisan is required, according to Applicant's argument, to ignore all of

this description of what to do with a skin cell and infer that the "patient's own cells" in the first sentence refers to stem cells harvested from bone marrow.

37. Continuing with Applicant's chosen texts, Page 49, line 30, to page 50, line 6 teaches:

> A growth factor (or gene or other genetic material) can be inserted into or onto the body to grow missing limbs or body parts. The insertion of a multifactorial and nonspecific growth factor (or gene) is required. Such a growth factor is pluripotent, senses what body part or other component is missing, and directs adjacent cells to reconstruct the body part along genetically predetermined pathways. The process is not unlike the salamander regrowing a severed tail or limb. Other growth factors may or may not be required.

38. Like pages 40-42, this section postulates incredible results. In this instance, a process of regeneration like that observed in salamanders is asserted to be achieved in human patients simply by inserting a "growth factor"; that all it takes. The growth factor is said to act upon adjacent cells, but the growth factor is not suggested to be a cell. Contrary to Applicant's assertion that "pluripotent stem cells are described at page 50" (Brief, p. 22), this section does not describe or suggest pluripotent stem cells.

39. While pages 47-48 suggest that stem cells can be used "in some cases", the specification does not specifically teach that stem cells should be used to grow an artery. While the hypothetical dedifferentiated skin cell and/or "germinal cells" might be pluripotent, they are not species of stem cells harvested from bone marrow, they are not species of any known stem cell, there is no evidence that they even exist, and the "guidance" does not teach one of skill in the art as to how to use them in the instantly claimed methods. In order to arrive at the claimed methods, one first has to select "growth of an artery" from among the several possible outcomes suggested, and then guess that the "some cases" where stem cells are utilized (p.48, line 13) refers to instances where one wishes to grow an artery. Even if that guess is made, no particular reason is given why the stem cell should be harvested from bone marrow—bone marrow is not

mentioned in the context of artery formation. Since the artisan is required to look elsewhere in the specification for guidance as to which cell to use, there is no particular reason to choose or not choose "the blood of the patient, or from cell culture techniques" (see pp. 40-42). The artisan could look to p.37, lines, 19-23, which teaches:

> "Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated. Likewise, any host cell, cloned cell, cultured cell, or cell would work."

Far from guiding the skilled artisan on how to perform a specific method, the most straightforward meaning of this teaching is that the skilled artisan should believe that any cell can do anything. The immediate context is related to eye formation (p. 37, lines 17-18), but the general context seems to be about formation of any desired tissue. The nearest mention of "artery" occurred two paragraphs preceding, on page 37, lines 8-16 (emphasis added):

> "Sticky cells can be used to attach genetic implants to selected sites. This is, for example, important when placing a soft tissue implant in or on a site of an *artery* wall. In this manner, an additional heart could be grown from a genetic implant. Once matured to a reasonable state, this new heart can be the body's primary heart and the old heart can be evacuated surgically. Any venous or *arterial* connections, reconfigurations, or ligations can be surgically attended to. Any other organ can be similarly produced at any desired site in soft or hard tissue."

40. Therefore, page 37, lines, 19-23 can be understood (if the malapropism of "cascade of genetic material" is ignored and the expression is taken to be equivalent to "genetic cascade") to suggest that the combined action of a hypothetical master control gene together with stem cells or "germinal cells" can result in the formation of any desired tissue. Besides being an incredible assertion, this is clearly not a specific teaching about artery formation. In this context, the sentence "Likewise, any host cell, cloned cell, cultured cell, or cell would work" would have the

skilled artisan believe that any cell can be made to form any tissue, which teaches away from any suggestion to specifically use stem cells to form an artery.

41. Finally, even if Applicant's desired choices were made, so that use of stem cells to grow an artery is contemplated, the specification does not teach one of skill in the art *how to* use stem cells to grow an artery. Applicant's argument is as follows (Brief, p. 27):

> Appellant disagrees with the PTO's position that even if Appellant's interpretation of the specification is reasonable, it does not teach one skilled in the art how to use stem cells for growing an artery. The specification teaches that the reimplanted stem cells effect organ growth via direct differentiation and morphogenesis (page 48, lines 13-15). The specification (page 45, lines 1-4) contemplates growing an artery in the "heart, legs or other areas." The specification contemplates using bone marrow aspirant harvested from a patient (pages 40-42) as a potential source of stem cells used for the promotion of organ growth. During reimplantation, stem cell aspirant obtained from a patient's bone marrow is returned to the patient by injection at a desired location to promote the growth of an artery via direct differentiation and morphogenesis.

42. As noted above, the section on pages 47-48 does not even teach how to use the explicitly exemplified skin or germinal cells to form an artery. Referring to pages 40-42, Applicant relies on the notion that because the specification suggests the growth of organs which comprise an artery, the specification teaches how to grow an artery. Of course growth of an organ encompasses an artery. Growth of an organ can also encompass growth of pancreatic islet cells or a heart (specification p.48, lines 3-4), a tooth, a kidney, or an eye (specification, pages 40-42). If stem cells can do all of these things, how does one control the process to specifically form an artery? Simply suggesting that stem cells can be used for promoting development of *an organ* does not teach one of skill in the art *how to* grow *an artery*. The specification does indeed contemplate growing an artery in the "heart, legs or other areas" at page 45, lines 1-4, but this specifically teaches administration of materials other than cells for this purpose:

> An artery can be grown in the heart, legs, or other areas by injecting a gene or other genetic material into muscle at a desired site.

Therefore, page 45, lines 1-4 do not even contribute to the concept of administering stem cells to grow an artery, much less provide enabling guidance for the method. The specification merely puts forth the idea that something can be done and then invites the skilled artisan to figure out how to do it.

43. As the stated goal of the claimed method includes "growing a new artery" it is important to consider what the specification teaches about growth of a new artery. The sections relevant to growth of a new artery on pp. 54, 56, and 62 of the specification are reproduced here:

44. p. 54:

> "After four weeks, another MRI is taken which shows the patient's leg artery. The MRI shows that (1) at the first site a new artery is growing adjacent the patient's original leg artery, and (2) at the second site a new section of artery is growing integral with the original artery, i.e., at the second site the new section of artery is lengthening the original artery, much like inserting a new section of hose in a garden hose concentric with the longitudinal axis of the garden hose lengthens the garden hose."

This section clearly distinguishes between growth of a *new artery adjacent to* an existing artery and growing a new *section* of an artery *integral with* the original artery. The instant claims recite "growing and integrating tissue", wherein the "tissue comprises a desired artery", which "integrates itself into said body" not "forming a new *section of* an artery." Therefore, the claims are clearly meant to encompass the result predicted for the first site as described above.

45. p. 56:

> "Anatomic evidence of collateral artery formation is observed by the 30th day following injection to the RAOTS construct. One end of the artery integrates itself in the heart wall to receive blood from the heart. The other end of the artery branches into increasing smaller blood vessels to distribute blood into the heart muscle. Once the growth of the

> new artery is completed, the new artery is left in place in the heart wall. Transplantation of the new artery is not required."

Once again, the "new artery" is described as first forming and then subsequently integrating.

46. p. 62:

> Similar results are obtained, i.e., a new section of artery grows integral with the original artery, and a new section of artery grows adjacent the original artery. The new section of artery has integrated itself at either end with the original artery so that blood flows through the new section of artery.

This section at p. 62 is ambiguous because it refers to two new sections of artery: one integral to existing artery, one adjacent to it. Thus, the antecedent for "the new section of artery" in the second sentence is unclear. Nevertheless, this section of p.62 suggests formation of a new structure that is not initially integral with the preexisting artery, but which subsequently integrates into an artery, as do each of the relevant sections of p. 54 and p.56.

47. Considering all of the evidence, it is reasonable to interpret the claims as encompassing not only extension of new sections of artery from preexisting arteries or arterioles, but also formation of entirely new arterial structures "in the middle of nowhere", so to speak. This mechanistic distinction is significant because the art teaches that post-natal arteriogenesis occurs by cell proliferation and remodeling of preexisting collateral arteries or arterioles. See, for example, Buschmann et al., News Physiol Sci. 1999 Jun;14:121-125, at Figure 2, and on p. 122, left column: "Arteriogenesis is the rapid proliferation of preexisting collateral arteries… It is important to recognize that this process is not a passive dilatation but one of active proliferation and remodeling." Thus, by teaching that new arteries, or sections of arteries, will grow adjacent to existing arteries and subsequently integrate, the instant specification teaches a novel process that is at odds with the prevailing understanding in the art. Therefore, prophetic Examples 18

(p.54), 19 (p.56) and 36 (p. 62) are not credible in the absence of a demonstration that such results did or would occur *in vivo*. No claim is enabled for a method that causes formation of entirely new arterial structures followed by integration into an existing artery. Furthermore, although post-filing publications describe methods and results that fall within the scope of the claims under consideration, none of these references support or suggest anything like the formation of a new artery structure which then integrates into an existing artery as taught in the specification. Therefore, no assertion that any post-filing reference confirms Applicant's disclosed and claimed results can be found persuasive if formation of a "new artery" is defined as in the specification at pages 54, 56, and 62.

48. Pages 54, 56, and 62 are within Examples 18. 19, and 36, which prophetically describe introduction of VEGF cDNA into a patient to induce angiogenesis. On 05/25/2007, Applicant entered into the record a method for extrapolation of dosages of a VEGF cDNA construct taught in Examples 18. 19, and 36 to calculate a number of stem cells to use in a method wherein stem cells are used in place of the cDNA construct, accompanied by declarations by Drs Lorincz and Heuser. The extrapolation method and its associated declarations have been addressed thoroughly in previous office actions, specifically the office action mailed 07/24/2007 at paragraphs 35-42, the office action mailed 05/05/2008 at paragraphs 34-38, and the office action mailed 02/26/2009 at paragraphs 24-28. Applicant, "even at the expense of engorging the instant Brief", again addresses this matter with five pages (pp.29-34) of arguments, most of which have been addressed in the record.

49. Applicant makes a series of related assertions with regard to the guidance present in the state of the prior art:

P. 29:

> Appellant used a well established weight basis conversion method employed in the medical art for decades to convert the gene dosage of Example 18 to cells. Appellant never argued the viability of conversion across all species lines.

P. 31:

> It is clear from such unfounded characterization that the PTO has paid no deference to the conversion practice used routinely for decades by the medical art.

P. 32:

> The PTO asserts at page 26, ¶27 of the Rejection that Appellant's post hoc derivation (extrapolation) is not implicit from any teachings in the specification. Such argument misses the point, which is that such extrapolations have been used for decades in the medical arts in regard to cell therapy and are part and parcel of the prior art. That which is well known in the art need not be included in Appellant's specification in order to comply with the enablement requirement of Section 112, first paragraph. See MPEP Section 2164.01.

P. 34:

> Appellant's evidence establishes as a material fact that physicians have long used conversion charts/formulas for estimating dosages of cells from nucleic acids.

50. The record shows that the calculation under discussion is not substantially analogous to well known methods of converting DNA amounts to cell numbers within a species cited by the Declarants. Applicant *has* argued the viability of conversion across species lines because the very basis of the calculation requires that the amount *a plasmid DNA construct,* which is recombinant molecule designed to express a single desired human gene linked to DNA found natively in bacteria, is used to calculate and number of human cells. The quantitative and qualitative differences between a plasmid construct and genomic DNA as it is found in cells have been discussed thoroughly in the record, e.g. the office action mailed 02/26/2009 at paragraph 25. It has been shown, for example, using the data from tables supplied by Drs. Lorincz and Heuser, that the amount of VEGF coding sequence in an equal mass of human genomic DNA

and VEGF plasmid DNA differs by a factor of 5.26 x10^5. Applicant has not refuted these findings, except to characterize them as "esoteric" (Brief, p. 30).

51. Applicant further asserts (Brief, p. 30):

> The PTO's statement that it is untrue that the medical art has used such conversions for the past fifty years in cell therapy because they "would not recognize the terminology or even imagine the concept of conversion depicted in Exhibit D" eschews a want of factual basis. The PTO rejection is devoid of any objective evidence supporting such a position. It is also apparent that Drs. Heuser and Lorincz disagree.

52. Applicant is again referred to the office action mailed 07/24/2007 at paragraph 38, wherein an online publication titled *Plasmids; Histories of a Concept*, was cited to establish that the term plasmid was coined in 1952. It was further pointed out that techniques for making cDNA (copy DNA made by reverse transcription of mRNA), and for using plasmid vectors propagate and express cDNA in cells were developed in the 1970s. Therefore, contrary to Applicant's assertion, it is well established by objective evidence that scientists 50 years prior to the filing date of the instant application (a time period cited in the Declarations filed 05/25/2007 at paragraph 6) would not recognize the terminology or even imagine the concept of the conversion under discussion. Furthermore, the record shows that Drs. Heuser and Lorincz concluded that the conversion depicted in Exhibit D is *consistent* with the extrapolations that have been performed for over 50 years. This carefully worded conclusion is not challenged. It remains undisputed, however, that the consistency extends only to the point that the extrapolations involve math and DNA; any further comparisons would be impossible.

53. Applicant places great significance on the coincidence of the cell numbers derived by the proffered calculation with cell numbers disclosed in post-filing publications:

> P. 30:

> However, the PTO has not sufficiently explained why the reasonableness of using such weight conversion appears to be supported by the fact that such converted dosages are commensurate with those used by workers in the art using bone marrow stem cells to grow an artery, such as that reported in Strauer.

P. 31:

> It is evident from the conversion of nucleic acid dosages to cell dosages that the converted cell dosages fall within the range specified by Isner. The reasonableness of the conversion has been previously demonstrated regarding a conversion of the dosage of Example 18 in the instant application to the bone marrow stem cell dosages specified by Strauer. Hence, the usefulness of the well-known and established weight conversion has been attested to and demonstrated in two diverse cases.

The footnote on page 31 describes a calculation in which the conversion method under discussion is applied to numbers disclosed the Isner '887 patent. The footnote states, "using 2,000 micrograms as a preferred dosage of nucleic acid described by Isner '887 one skilled in the art applying Appellant's calculus could extrapolate to a cell dosage of about $50x10^6$, which falls within the range specified for cells by Isner '887". This ignores the fact that Isner teaches: "Effective amounts of DNA are between about 1 and 4000 μg, more preferably about 1000 and 2000, most preferably between about 2000 and 4000", and "Generally, from about 10^6 to about 10^{18} progenitor cells are administered to the patient for transplantation" (column 11, lines 4-9 and column 7, lines 17-23, respectively). Note that Isner teaches a 4000-fold range of μg DNA and a *trillion-fold range* (10^6 to about 10^{18}) of cells. This shows that even if using the amount of plasmid DNA to calculate a number of eukaryotic cells were a legitimate procedure, the formula for doing so based on Isner's numbers would not be the simple ratio Applicant has presented. This supports the rejection of record, which finds that any relationship between the results of Applicant's formula and any cell number taught in Isner '887, or in any post-filing art, is coincidental. It is neither surprising nor convincing that a formula could derive a value within the

trillion-fold range of cells taught by Isner. Furthermore, there is no evidence that Isner, an acknowledged author and inventor in both gene therapy and cell therapy, saw any significant relationship between the disclosed amounts of plasmid DNA and numbers of cells.

54. Applicant argues (p. 33) that it is a mistake to refer to the calculation as "Applicant's formula." This is not persuasive because the record shows that Applicant has in fact referred to the calculation as "Appellant's conversion". Applicant further asserts that the "PTO's challenge in regard to the technical basis underlying the conversions is misdirected. Such challenge should be directed toward the originators of this well known medical tool and workers in the art who used such alleged faulty calculus." One can only ask, "Who are these originators and workers?" It is clear from the facts presented herein and in the rejections of record, that the method under discussion, which purports to extrapolate an appropriate cell number for administration from the quantities of plasmid DNA, is Applicant's *post hoc* derivation. It is not present in the application as filed. It is not implicit in the teachings of the specification. It is not substantially analogous to well known methods of converting DNA amounts to cell numbers within a species cited by the Declarants. It is not information that is already known by those skilled in the medical arts. Applicant has been advised that if an example of the use of the amount of recombinant plasmid DNA in a gene therapy protocol to extrapolate the number of stem cells to use in a cell therapy procedure were to be found in the peer-reviewed scientific literature or the patent literature, the Examiner's position would be refuted. There is, however, no example of this calculation in the prior art or post-filing art. There is no rational basis for proposing that a person of skill in the art at the time the instant application was filed would even think of performing this calculation

without being specifically prompted to do so. The instant specification does not provide that prompting.

55. Applicant has pointed out that MPEP Section 2164.01 (c) states that it is not necessary to specify the dosage if one skilled in the art could determine such information without undue experimentation. If present, a recommended dosage would be understood as guidance to be considered along with the other factors in the enablement analysis. The present rejection, as originally set forth, however, did not specifically mention the absence of guidance as to how many stem cells should be used to grow an artery. Cell dose has never been cited as single, critical factor for determining enablement. Applicant has argued that stem cell overdosing has not proved to be problematic and that safe dose ranges have been established over years of medical practice directed to bone marrow transplant cell therapy (Brief, p.34). In the face of this, one might ask why Applicant has chosen to bring the calculation into the discussion. The answer appears to be that Applicant seeks to persuade the Examiner, or the Board, that the specification is far more definitive in its teaching than it actually is. The fact remains that Examples 18, 19, and 36 of the instant specification are prophetic examples in which VEGF cDNA is introduced into a patient to induce angiogenesis Examples 18, 19, and 36 do not direct the skilled artisan to use any kind of cell in place of the VEGF cDNA in the examples. They do not suggest the use of stem cells or any kind of cell, or suggest any method wherein cells are administered to grow an artery or any other organ. Guidance for the use of cells is not present in Examples 18, 19, and 36, not even implicitly.

56. Further with respect to the guidance provided by the specification, Applicant repeatedly asserts that the specification describes stem cells as being able to promote tissue growth or formation of an artery through "differentiation and morphogenesis" (Brief, pages 5, 9, 10, 14, 21, 22, 25, 27, 28, 41, 49). Examples include:

Brief, page 5:

> The specification describes the subject matter of claims 407-410 at pages 40--42 and pages 47-52, wherein the specification discloses using a patient's own stem cells for growing multiple described organ species, through differentiation and morphogenesis.

Brief, page 24:

> PTO's statement that the specification fails to "provide any guidance as to how to use stem cells to grow an artery" evinces a lack of understanding of how differentiation and morphogenesis occurs in vivo. No guidance is necessary because the art skilled would recognize that once the stem cells are implanted, artery growth proceeds along genetically predetermined pathways.

Brief, page 25:

> In any event, the disclosure at page 47, line 22 through page 48, line 15 of the specification clearly rebuts the PTO's notion that Appellant never clearly enunciated using stem cells (harvested from bone marrow and blood) for promoting direct differentiation and morphogenesis into an organ.

Brief, page 26-27:

> Apparently, the PTO originally failed to consider the following two paragraphs from page 48 of the specification:
>
> > During reimplantation one of the patient's own cells is returned to the patient. During implantation, a cell not originally obtained from the patient is inserted on or in the patient.
> >
> > In the example above, if germinal cells (and in some cases, stem cells)are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.
>
> The specification teaches that the reimplanted stem cells effect organ growth via direct differentiation and morphogenesis (page 48, lines 13-15).
>
> During reimplantation, stem cell aspirant obtained from a patient's bone marrow is returned to the patient by injection at a desired location to promote the growth of an artery via direct differentiation and morphogenesis.

Brief, page 28:

> Appellant submits that the specification clearly enables one skilled in the medical arts to select and obtain bone marrow aspirant from a patient and to reimplant such aspirant at a desired site in said patient to promote artery growth via direct differentiation and morphogenesis along genetically predetermined pathways.

57. Ziegelhoeffer et al., (*Circulation Research.* 2004;94:230-238) studied the fate of GFP-labeled bone marrow cells transplanted into lethally irradiated recipients in a mouse model of hindlimb ischemia. The results showed that donor cells accumulate around growing collateral arteries and in ischemic tissues, but the donor cells do not become incorporated into endothelium or tunica media of the vessels. The authors concluded that bone marrow-derived cells do not incorporate into vessel walls, but may function as supporting cells (see Abstract). Therefore, even if Dohmann 2005, Strauer 2002, or other post-filing disclosures teach that administration of bone marrow cells causes the formation of an artery, the process is not through direct differentiation and morphogenesis as taught in the instant specification. Thus, the post-filing disclosures do not confirm these teachings, but instead the post filing evidence indicates that administered bone marrow cells, which would include some stem cells, do not differentiate into the cells of which arteries are made. In particular, the prediction that "if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (specification p.48, lines 13-15) has been shown not to be true when the source of stem cells is a mixed population of bone marrow cells and the organ under consideration is a new artery.

58. Applicant asserts (Brief, p. 39) that Strauer confirms the teachings of the instant specification, and further asserts that Strauer speaks to the question of whether undue experimentation would be required:

> "…the post-filing Strauer publication performs the same steps as claimed and achieves the same results. The record will show that when repeatedly challenged by Appellant to point out where Strauer performed any experimentation, the PTO was not able to identify any such alleged experimentation. Strauer does not describe using any experimental protocol to determine appropriate cell population, i.e., there is no requirement for using a specific subset of bone marrow stem cells. Regarding time of treatment, Strauer does not disclose that determining time of treatment required experimentation.

59. Similarly on p. 37:

> Appellant has consistently taken the unanswered position that Strauer, relied upon by the PTO, describes little if any experimentation required to practice the disclosed implantation of bone marrow stem cells.

60. And on p.40:

> Appellant believes that the above-mentioned lack of experimentation by Strauer actually demonstrates the converse of the present PTO Examiner's hypothesis, i.e., that one skilled in the art would be able to make and use Appellant's so-called "plausible" invention without recourse to experimentation of any kind, let alone an undue amount of experimentation.

61. Strauer et al. 2002 state clearly and in detail that cell population is critical at pp. 1916-1917. This determination of a critical cell population has been held to be an example of the experimentation that would be required before achieving any repair of dead/damaged heart tissue. Strauer et al. state on p. 1916:

> "The most crucial questions we had to address while designing and realizing this trial were: (1) What cell population should we deliver? (2) Which application method is the most efficient? (3) When should the cells be transplanted?" (Emphasis added).

On page 1916, left column, and in the paragraph bridging pages 1916-1917, Strauer et al. reviewed prior work in which various cell fractions were studied or observed to into specific cells types that can contribute to cardiac repair. In so doing, Strauer et al. cited about 20 papers, all but one of which were published after the filing date of the instant application. (The exception dealt with transplantation of skeletal myoblasts, see ref. 25 in Strauer et al.) It is inexplicable how Applicant could read this and conclude that this publication fails to reveal any teaching that experimentation was required to determine cell population. Strauer explicitly teaches that the decision to use the whole mononuclear cell fraction from bone marrow aspirates was made after consideration of several published studies involving various subfractions (paragraph bridging pages 1916-1917). Therefore, Applicant's later statement, "Strauer does not describe using any experimental protocol to determine appropriate cell population, i.e., there is no requirement for using a specific subset of bone marrow stem cells" (Brief, p. 39, emphasis in original), is misleading. The emphasized conclusion can be reached only in view of Strauer's results and the work of others cited by Strauer. In contrast, the instant specification shows no evidence of awareness that the sub-populations of stem and progenitor cells discussed by Strauer et al. are even a matter of concern.

62. Similarly, Applicant asserts that "Strauer does not disclose that determining time of treatment required experimentation" (Brief, p. 39). Time of treatment was deemed by Strauer et al. to be an important consideration, as noted above and in the record. Again, Strauer et al. considered published results of experimentation performed by others to decide upon a time of administration for their own protocol, which was itself experimental (p.1917, paragraph bridging the columns and next paragraph). The cited references were all published after the filing date of

the instant application, except for a 1956 review on wound repair (see refs 35-40 of Strauer et al., 2002). Thus, it is clear that the question of when to administer cells was the subject of much experimentation after the filing of the instant application but prior to the Strauer et al. 2002 publication. Strauer et al. 2002 concluded, "Although the ideal time point for transplantation remains to be defined, it is most likely between days 7 and 14 after the onset of MI" (p.1917, right column. Applicant asserts that a later publication of Strauer et al. ("Strauer 2005" of record) discloses treating chronic MI in patients that had transmural MI some 27 months earlier and that this later publication is the "best evidence" in regard to whether time of treatment in human patients is critical (Brief, p. 41). This shows that *as experimentation continues*, understanding of the process improves. Thus, we find that the instant specification is silent on the subject of timing of cell administration to grow an artery and the "best evidence" in regard to time of treatment only became available approximately 7 years after the instant application was filed. These facts support the rejection of record, which finds that post-filing references of record, such as Strauer et al. 2002, constitute evidence of the further act of invention that was required before achieving the claimed results. Any amount of experimentation, such as the work performed or cited by Strauer, regarding what cell population to use, what delivery method to use, and when cells should be transplanted, would be infinitely more than is presented in the instant specification in support of the claimed methods.

63. The office action mailed 02/26/2009 cited two internet articles published in The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, entitled, "Tissue Engineering and Interventional Cardiology" and "Progenitor Cell Transplantation and Function following Myocardial Infarction." Applicant points out that the copies furnished by the Examiner contain less than the

complete content of the published articles and argues that full consideration of omitted portions would not support the findings of the rejection of record. The Examiner acknowledges that the documents were incomplete due to a previously unrecognized error in converting the web pages to pdf format. The text of the rejection included a quote that was not reproduced on the copies provided (e.g. the final quote from participant O'Neill, "…bone marrow is unfiltered…Basically, the injection contains the "kitchen sink"…), which shows that the Examiner intended to provide the full documents. However, even when the complete documents supplied by Applicant are considered, it remains true that the concerns addressed by the participants in these discussions that took place about seven years after the instant specification was filed are the same as those raised herein and in the rejections of record with respect to the lack of guidance provided by the instant specification. It is clear that questions of choice of cell, dosing, timing, means of delivery, and cell survival, were still unanswered in these discussions that took place about seven years after the filing of the instant application. It remained uncertain what the critical cell in the preparations administered in the intervening art is; it may not be any previously characterized stem cell, it may not even be a *stem cell* at all but rather some other previously uncharacterized growth factor secreting cell. The wisdom of transplanting an uncharacterized mixture of cells was in question (see comments by participants O'Neill, Dangas, and Holmes). The net effect of the multiple uncharacterized factors secreted by transplanted cells was still unknown and considered to be unpredictable (see comment by participant Dangas). Participant Witlow's comments are noteworthy if the selected site for growth of a desired artery is the heart and in view absence of any specific guidance as to how many cells to deliver in the instant specification; the non-toxicity of administered cells is apparently not predictable in the situation

of attempting to repair a damaged heart, regardless of whether Dr. Witlow's concerns are ultimately substantiated or dismissed. These questions remained even though the participants were well aware of post-filing disclosures of record; Strauer was specifically cited. Clearly, considerable experimentation had taken place and several participants suggested that more experimentation was needed.

64. It was further noted that one of the participants in these discussions was Dr. Richard Heuser, a Declarant of record in the instant case. Applicant complains that the previous office action did not quote Dr. Heuser's comment "The first time I saw this technique presented by the group in Frankfort, I was astonished at how simple it actually was." It should be noted however, that Dr. Heuser went on to say, "Some of these therapies make good sense for the individual patient, but **more study data are needed**." Thus, Dr. Heuser apparently agreed with the preponderance of commentary, which indicates that the simplicity is more apparent than real. The rejection also posits that *if Applicant's arguments are to be accepted*, then Dr. Heuser, having "read and understood" the instant specification, was in possession of answers to the controversies under discussion. *If so*, Dr. Heuser could have informed his colleagues that enabling guidance for a method for growing and integrating a new artery at any desired site by injecting stem cells had been worked out about seven years prior to the time the published discussions were taking place. Dr. Heuser could have clarified matters without divulging any confidential information by directing his colleague's attention to Patent Application Publication 20040071637, which is continuation of instant specification and was published on April 15, 2004, or Patent Application Publication 20020192198, in which substantially similar disclosure

was published on December 19, 2002, or Patent Application Publication 20030044396, in which substantially similar disclosure was published on March 6, 2003.

65. Applicant (Brief, p. 39) asserts that "once one skilled in the art realizes that bone marrow promotes the growth of arteries the delivery of the bone marrow is simple." It is clear from the discussion published in The Journal of Invasive Cardiology, as well as from the other post-filing references of record, however, that many of the critical decisions, manipulations, and preparations take place before the injection is made. Clearly, simply knowing how to inject cells is not enough to perform a method of growing a new artery. This further illustrates that a claim to a method of growing an artery by administering a *stem cell* should be supported by more than a vague enunciation of the concept. Furthermore, all arguments that post-filing successes reported by others were predictable and did not require much experimentation are thoroughly refuted. Therefore, this rejection finds that the post-filing references do not "confirm" the teachings of the instant specification, as asserted by Applicant. Instead, the post-filing references constitute evidence of the further act of invention that was required before achieving any growth of an artery by administering cells.

66. Regarding the presence or absence of working examples in the specification, it has been noted in the record that the present specification does not disclose even a single enabled embodiment of the claimed method. The instant specification does not show a single organ, part of an organ, tissue, artery, or even a bud, formed by placing cells in a body. Applicant's Brief addresses the issue of examples on pages 34-36. Applicant accurately points out that prophetic disclosures are permitted under the rules, statute, and case law. However, the fact that prophetic examples are *permitted* does not mean that any particular set of prophetic examples is adequate

for enabling for the claims under consideration. Applicant's most favorable interpretation of the instant disclosure is that, by circuitous logic not explicitly presented in the disclosure, one of skill in the art might surmise that a method to use autologous stem cells to grow an artery was suggested. For example, upon reading juxtaposed excerpts of the specification (not the complete specification), together with claims that were not present in the application as filed, the Declarants of record have been willing to say: "The disclosures referenced in above Paragraph ... of the specification *relate to* using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery" (emphasis added)." A disclosure that makes it possible to piece the claimed generic concept together is not the same as an enabling disclosure.

67. According to Applicant's earlier arguments, the issued Isner '887 and Kornowski '832 patents indicate that Dr. Elia's improvement to the medical arts has fostered prejudicial skepticism because of its manner of reduction to practice. The gist of Applicant's argument is that the Isner '887 and Kornowski '832 patents were allowed with claims to treatment of humans that were supported only by prophetic examples and, therefore, the prophetic examples of the instant case should also be considered sufficient. Applicant still claims to not understand the finding of record that the examples in the patents are not prophetic, even though they do not disclose human clinical trials (Brief, p. 35). The record shows that the examples that support the allowed claims are not prophetic because they are based on work actually performed and results actually achieved, which is the definition of a working example. See MPEP 2164.02. The Isner '887 and Kornowski '832 patents illustrate that patents in which biotechnological inventions are directed to the treatment of humans can rely on animal, or even in vitro, evidence. Applicant

points out that many animal experiments are not replicated when applied to humans and argues that this means that "such patents were considered to be enabled by the PTO despite the lack of working examples directed to human patient, such as those generated during clinical trials." This is not persuasive because the standard applied by the PTO calls only for a reasonable correlation recognized in the art, not absolute predictability. The sufficiency of the evidence is determined on a case-by-case basis. The instant specification provides no evidence comparable to that in the Kornowski '832 patent upon which to base a judgment. Furthermore, it is difficult to see how the fact that animal studies are not perfectly predictive of human responses, supports the argument that the instant claim should be considered enabled when they are supported by no data at all.

68. With respect to compliance with 35 USC 112, first paragraph, the entire claim has weight, including statements of purpose and intended outcome recited in the preamble or in 'wherein' clauses. Therefore, in the instant case, the claims must be enabled for growing and integrating an artery. Questions of which cells to use, how many to use, when to administer the cells, and whether the disclosed results are confirmed by post-filing disclosures, might have been clarified by working examples in the specification. Even the disclosed prophetic examples are not specifically directed to the claimed subject matter. The absence of specific examples is a contributing factor because a prophetic example based on predicted results rather than work actually conducted can support enablement only if the claimed results are actually predictable. Case law cited in the record confirms that chemistry, biology, medicine, and physiology have been consistently recognized as unpredictable arts. It has been established herein and in the record that Examples 11-18, 19, and 36, cited by Applicant as supporting the enablement of the instant claims, not only lack support by experimental evidence, they prophetically teach

unpredicted, even incredible, results. It has been established herein and in the record that post-filing disclosures show that extensive experimentation has been required to achieve results that fall within the scope of the asserted claims. Regardless of how straightforward the practice of the claimed invent may be, the instant specification does not establish with any reasonable certainty how to select the cells that will form an artery, or whether administration of any of the cells mentioned in the specification will form an artery. The instant specification asserts many remarkable results but does not show a single organ, part of an organ, tissue, artery, or even a bud that has been formed by merely placing cells in a body. The present specification does not disclose even a single enabled embodiment of the claimed method. Thus, Applicant's assertion (Brief, p. 48) that "the materials and administration techniques, but not the inventive results, were well known when the instant application was filed" is not persuasive: There are no inventive results.

69. On pages 43-47 of the Brief, Applicant again alleges that the Declarations of Dr. Meger, Dr. Heuser and Dr. Lorincz had not been given due consideration. Case law has established that anticipation and operativeness are questions of fact; however, obviousness and enablement are questions of law. See In re Lindell, 155 USPQ 521; In re Chilowsky, 134 USPQ 515. The underlying basis for the legal conclusion has been considered herein and in the record. Dr. Heuser and Dr. Lorincz have been willing to say: "The disclosures referenced in above Paragraph ... of the specification *relate to* using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery" (emphasis added)." That is, the Declarants managed to piece the general idea of the instant claims together. According to the Declarations, this general conclusion was based

upon reading juxtaposed excerpts of the specification (not the complete specification) together with claims reciting administration of stem cells to grow an artery, which were not original to the application as filed. The Declarants followed this conclusory statement *an opinion as to the ultimate legal conclusion of enablement*, to which no weight is given. A disclosure that makes it possible to piece the claimed generic concept together is not the same as an enabling disclosure. The sections of the specification cited in the declarations have been thoroughly considered, along with the entire disclosure, herein and in the record. The thread that connects the pieces of the generic concept also runs through hints of non-existent methods, unidentifiable cells, nonsensical method steps, and most importantly, predictions of results that are either incredible or directly contradicted by subsequent disclosures. Besides not having legal weight, Declarants' conclusory statements regarding predictability and the amount of experimentation required are thoroughly refuted by the references cited herein and in the record. Even though administration of cells, and apparatus therefor, were known in the medical art at the time of the present invention, the evidence presented herein and in the record shows that simply knowing how to inject cells is not enough to perform a method of growing a new artery. The choice of cell to be administered to achieve the recited outcome was not known in the prior art, it is not clearly described in the specification, and it remains a subject of controversy long after the instant disclosure was filed. Therefore, the Declarations of record are not sufficient or convincing to overcome the instant rejection.

70. Applicant (Brief, p. 42, 47, 48) compares the instant case to *in re Wands*, generally arguing that the "instant fact situation is similar to that of *In re Wands* because the skill level is also high and known administration techniques and known materials are also utilized in the

practice of the invention." Applicant again refers to the expert opinion declarations of Drs. Heuser and Lorincz. Applicant urges that proper consideration of all of these factors compels a conclusion that undue experimentation would not be required. This has been fully considered but is not found to be persuasive. In *Wands*, the sole issue was whether, in that particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies against HBsAg (*In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1404). The facts showed that **inventor Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations** (*In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1407). The court ruled that that it would not require undue experimentation to make and use the claimed immunoassay method. The court in *Wands* stated that enablement is not precluded by the necessity for some experimentation such as routine screening. (*In re Wands*, 8 USPQ2d 1400 at p. 1404). The facts in the present case are substantially different from those of *Wands*. In the instant case, what is missing is well beyond routine screening. Unlike the monoclonal antibody art, the art of stem cell therapy is not as highly developed and success is not predictable. The specific outcomes recited in the instant claims are unprecedented and the record shows that extensive experimentation has been performed by others in order to achieve methods that fall within the scope of the instant claims. The working examples in *Wands* were deemed sufficient to provide adequate guidance in view of the skill in the art and the already advanced development of the technology (*In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1406). In contrast, the instant specification presents no working examples directed to the claimed methods, as noted herein and in previous office actions. The prophetic examples not only lack support by experimental evidence, they predict results that are

either incredible or directly contradicted by subsequent disclosures. Therefore, the only *Wands* factor weighing in favor of enablement is the level of skill in the art, which is relatively high. It follows that, unlike *Wands*, the instant disclosure does not enable the skilled artisan to make and/or use the claimed invention without undue experimentation.

71. It is easy to predict that if one injects cells into a body, *something* will grow therefrom; it might even be an artery—even tumors have arteries. Such a prediction however, does not meet the legal standard for enablement. As stated in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis." It has been stated repeatedly in the record that the courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997). While evidence of a fully developed clinical procedure is not required for a patent, the notion that the claimed new result, artery growth, can be achieved using old materials (bone marrow stem cells) and old methods (injection), was indeed "a germ of an idea" at the time the instant

application was filed. The instant specification does not even clearly enunciate this germ of an idea, let alone provide an enabling disclosure of how to make and use the claimed invention.

Double Patenting

72. The record shows that claims 403-405 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 163 and 170-173 of copending Application No. 10179589. Applicant has noted this rejection and expressed intent to file a terminal disclaimer upon an indication of allowable subject matter (Brief, p. 50). In reviewing the record, the Examiner finds that the grounds of rejection are fully set forth in a corresponding rejection mailed 11/03/2009 in copending Application No. 10179589. However, the Examiner has been unable to find in the instant application a complete statement of the "reasons of record" that is fully applied to all of the appropriate pending claims as they are currently amended in the instant and copending applications. It is further noted that the office action mailed 02/26/2009 in the instant application included an additional provisional nonstatutory obviousness-type double patenting rejection intended to reject additional instant claims not previously rejected over claims of 161-164 and 172-174 copending Application No. 10179589. The first sentence of this second rejection listed the claims of the present case incorrectly, which prompted Applicant to persuasively argue that the rejection is moot for being directed to canceled claims, and redundant for failing to address claims that were not already rejected (Brief, p. 50). To clarify the record, all prior double patenting rejections are hereby withdrawn in favor of the following.

73. Claims 403 and 407-412 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 161-164 and 172-174 copending Application No. 10179589. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

74. The respective independent claims 174 and 403 recite nearly identical methods of producing and integrating an artery at a selected site in a body of a human patient comprising placing a stem cell in a body of a human patient and growing said desired artery. Step (b) of claim 403 recites an additional step of forming a bud. Applicant's intended meaning for step (b) was indicated in remarks filed 11/28/2007 in the instant case: "the only step required by the practitioner is that of injecting stem cells into a selected site in a patient's body. Once injected, the stem cells interact with the human host by differentiating along predetermined physiological developmental pathways to form a vascular bud which grows into an artery." Therefore, Applicant indicates that step (b) inherently occurs every time step (a) is performed. Alternatively, if the claim is interpreted such that there are instances where a bud is formed and instances where a bud is not formed, copending claim 174 is generic to instant claim 403 in this regard. Therefore step (b) does not distinguish the claims. Copending claim 174 requires locally *placing* a stem cell in the body of a human patient while claim 403 requires locally *injecting* stem cells. As placing is broader than injecting, the independent claims are not identical, but are merely obvious variants of one another. Dependent copending claims 161-164, 172 and 173 in this case and instant claims 407-412 add identical limitations to their identical base claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

75. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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